

CLINICAL PRACTICE

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Depression in the Primary Care Setting

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This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 45-year-old woman with hypothyroidism that has been treated with a stable dose of levothyroxine presents to her primary care provider with depressed mood, negative feelings about herself, poor sleep, low appetite, poor concentration, and lack of energy. These symptoms began several months ago during a conflict with her partner. Although she has been able to continue with work and life responsibilities, she feels sadness most days and occasionally thinks that she would be better off dead. How would you evaluate and treat this patient?

THE CLINICAL PROBLEM

DEPRESSION IS A CLINICALLY SIGNIFICANT AND GROWING PUBLIC health issue. In 2015, depressive disorders were estimated to be the third leading cause of disability worldwide.¹ In the United States, the estimated lifetime risk of a major depressive episode now approaches 30%.² The incidence of suicide — which is associated with a diagnosis of depression more than 50% of the time³ — has been increasing and is the 10th leading cause of death in the United States.⁴

Major depressive disorder is a heterogeneous condition with a variety of presentations and a broad constellation of associated symptoms. The criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition,⁵ for diagnosing and rating the severity of major depressive disorder are listed in Table 1. The pathophysiology of depression remains incompletely understood. Decreased functioning of monoaminergic neurotransmitters (serotonin, norepinephrine, dopamine, or all of these neurotransmitters) in the brain has traditionally been implicated, with presumed correction of these functional deficits in response to effective antidepressant therapies. As the understanding of depression evolves to implicate processes of neuroplasticity — that is, functional changes, structural changes, or both in the brain in response to the environment and experience — such monoaminergic mechanisms are seen in the context of a host of molecular and cellular mechanisms that mediate human emotion.⁶

The onset of major depressive disorder is bimodal; most patients present in their twenties,⁷ and a second peak occurs in the fifties.⁸ Women are twice as likely to have depression as men.⁹ Other risk factors for the development of major depressive disorder include being divorced or separated,¹⁰ previous episodes of depression, elevated levels of stress, a history of trauma, and a history of major depressive disorder in first-degree relatives.⁵ In patients with major depressive disorder, coexisting anxiety, psychotic symptoms, substance abuse, and borderline

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KEY CLINICAL POINTS

DEPRESSION IN THE PRIMARY CARE SETTING

- Screening for depression and suicidal thinking and behavior is important in the primary care setting.
- Distinguishing between bipolar disorder and major depressive disorder is critical for treatment selection.
- The first-line treatment for mild depression is psychotherapy and symptom monitoring.
- Antidepressant drugs have been shown to have a favorable benefit–risk profile in moderate-to-severe depression. Psychotherapy may also be a first-line choice for moderate depression.
- The choice of treatment depends on associated side effects, the presence of coexisting conditions, specific symptoms, and the patient's history of response.

personality disorder are associated with a poorer prognosis, as well as a longer duration of episodes and greater symptom severity.⁵ In particular, the overlap between depression and anxiety has been well established; more than 50% of patients with depression report clinically significant anxiety and have greater refractoriness to standard treatments than patients who have depression without anxiety.¹¹

Primary care providers are important in recognizing and managing depression. An estimated 60% of mental health care delivery occurs in the primary care setting,¹² and 79% of antidepressant prescriptions are written by providers who are not mental health care providers.¹³ One study showed that among persons who have attempted suicide, 38% visited a health care provider within the previous week, and 64% visited a health care provider within 4 weeks before the attempt; most of these patients visited a primary care practice.¹⁴ Despite efforts to educate patients, communities, and medical professionals, stigma remains a primary barrier to recognizing and providing treatment for mental illness.¹⁵

STRATEGIES AND EVIDENCE

SCREENING

Universal screening for depression in all adult patients in the primary care setting, including pregnant and postpartum women, has been recommended by the U.S. Preventive Services Task Force.¹⁶ The Joint Commission recommends screening for suicidal ideation in patients in all medical settings.¹⁷ Brief screening instruments for depression such as the Patient Health Questionnaire 2^{18,19} and the Ask Suicide-Screening Questions²⁰ (Fig. 1) may be effectively and efficiently administered in the outpatient setting. Although some past studies suggested that screening for depression and suicide was not

cost-effective, more recent studies have shown that cost-effectiveness ratios for outpatient and emergency-department screening were on par with preventive interventions for other medical conditions,^{21,22} perhaps because of the use of more efficient screening tools and the increased incidence of these conditions.

ASSESSMENT

Potential causative or contributing medical diagnoses are a core consideration in the initial assessment of patients who present with any psychiatric symptoms. In the general hospital setting, up to one third of patients who present with depressive symptoms may have an underlying medical condition.²³ For instance, manifestations of dementia and delirium, including loss of social interactions, negative mood states, and cognitive dysfunction, may be similar to those of major depressive disorder. Multiple other medical conditions have been associated with depressive symptoms; these conditions include anemia, hypothyroidism, seizures, Parkinson's disease, sleep apnea, deficiencies of vitamins such as B₁₂ and folate, and infectious diseases such as human immunodeficiency virus (HIV) infection, syphilis, and Lyme disease.²⁴ In some cases, treatment of these underlying conditions may decrease or resolve depressive symptoms.

Because both prescribed and illicit substances can also result in depressive symptoms, the patient history should include assessment of the use of drugs such as beta-blockers, barbiturates, anabolic steroids and glucocorticoids, statins, hormones (e.g., oral contraceptives), levodopa and methylodopa, opioids, and some antibiotics (e.g., fluoroquinolones, mefloquine, and metronidazole).²⁵ Illicit use of or withdrawal states associated with marijuana, sedatives or hypnotics, opiates, cocaine, or stimulants may also lead to depressive symptoms.

In addition to a comprehensive history and physical examination, laboratory testing should be considered in any initial evaluation of patients with depressive symptoms. Although empirical data supporting particular tests are generally scant, initial screening tests should include complete blood counts and differential blood counts, basic metabolic studies, thyroid-function tests, and levels of vitamin B₁₂ and folate. Other laboratory tests such as liver-function tests, testosterone levels (in men), a Lyme titer, a rapid plasma reagin test, an HIV test, and urine and serum toxicologic screening should be considered as clinically appropriate.

In addition, a detailed psychiatric interview is important to accurately characterize psychiatric symptoms and assess the effect of symptoms on functioning. Establishing an effective therapeutic alliance with the patient requires sufficient time and attention to matters of a sensitive nature. Family, friends, partners, and other health care providers may be valuable sources of information; in nonemergency circumstances, patient permission is required to contact these persons. Consideration of cultural, social, and situational factors may help to identify relevant stressors, precipitants, or other situational variables that can affect functioning and guide decisions regarding treatment.

Other possible coexisting psychiatric diagnoses should also be considered. In particular, major depressive disorder should be distinguished from bipolar depression. Bipolar disorder, which is defined by current or past manic or hypomanic episodes, often presents as a depressive episode.²⁶ Because the clinical presentation of bipolar depression may be clinically indistinguishable from that of major depressive disorder, the diagnosis hinges on an assessment of past hypomanic or manic episodes (Table 1). This distinction also has therapeutic significance, since the use of antidepressants in bipolar depression without concurrent treatment with a mood stabilizer is associated with an increased risk of manic symptoms (i.e., “switching,” or depression turning into hypomania or mania).

TREATMENT

General agreement exists regarding the initial treatment of mild-to-moderate major depressive disorder in adults.²⁷ For mild depression, initial preference should be given to psychotherapy and symptom monitoring, with pharmacotherapy re-

Table 1. DSM-5 Criteria for Major Depressive Disorder.*

Criteria

Five or more of the following symptoms during the same 2-wk period, with the symptoms representing a change from previous functioning and with at least one of the symptoms being either depressed mood or loss of interest or pleasure in activities of daily life (symptoms that are clearly attributable to another medical condition are not included).

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (In children and adolescents, a depressed mood can be an irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of >5% of body weight in a month), or decrease or increase in appetite nearly every day. (In children, failure to gain expected weight should be considered.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

Severity of depression

Mild depression: Few, if any, symptoms in excess of those required to make the diagnosis are present, the intensity of the symptoms is distressing but manageable, and the symptoms result in minor impairment in social or occupational functioning.

Moderate depression: The number of symptoms, intensity of symptoms, functional impairment, or all of these variables are between those specified for “mild” and “severe.”

Severe depression: The number of symptoms is substantially in excess of that required to make the diagnosis, the intensity of the symptoms is seriously distressing and unmanageable, and the symptoms markedly interfere with social and occupational functioning.

A comprehensive assessment of depression should not rely simply on a symptom count but should take into account the degree of functional impairment, disability, or both.

* In contrast to major depressive disorder, the diagnosis of bipolar depression is based on the occurrence of a past or present hypomanic episode (symptoms present ≥ 4 days) or manic episode (≥ 1 week). A hypomanic episode involves elevated, expansive, or irritable mood; grandiosity; decreased need for sleep; pressured or increased speech; flight of ideas or racing thoughts; distractibility; increased goal-directed activity; psychomotor agitation; or excessive involvement in activities with high potential for painful consequences. The criteria for major depressive disorder are from the American Psychiatric Association.⁵ DSM-5 denotes *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.

served for cases of insufficient improvement. Psychotherapy, pharmacotherapy, or both should be considered for moderate depression.²⁸ Con-

A Patient Health Questionnaire 2

Over the past 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	0	1	2	3
Feeling down, depressed, or hopeless	0	1	2	3

B Ask Suicide-Screening Questions

	Yes	No
1. In the past few weeks, have you wished you were dead?	<input type="checkbox"/>	<input type="checkbox"/>
2. In the past few weeks, have you felt that you or your family would be better off if you were dead?	<input type="checkbox"/>	<input type="checkbox"/>
3. In the past week, have you been having thoughts about killing yourself?	<input type="checkbox"/>	<input type="checkbox"/>
4. Have you ever tried to kill yourself? If yes, how? _____ When? _____	<input type="checkbox"/>	<input type="checkbox"/>
5. Are you having thoughts of killing yourself right now? If yes, please describe: _____	<input type="checkbox"/>	<input type="checkbox"/>

Figure 1. Depression and Suicide Screening Tools.

On the Patient Health Questionnaire 2 (Panel A), a score of 3 or higher is 83% sensitive and 90% specific for a diagnosis of major depression. On the Ask Suicide-Screening Questions (Panel B), if the patient answers “no” to all four questions 1 through 4, the screening is complete and it is not necessary to ask question 5. No intervention is necessary (clinical judgment can always override a negative screening test). If the patient answers “yes” to any of questions 1 through 4 or declines to answer, the screening test is considered to be positive, and question 5 should be asked to assess severity. If the patient answers “yes” to question 5, the test is considered to be positive with an imminent risk identified. The patient requires immediate safety and a full mental health evaluation and cannot leave until he or she is evaluated for safety. Keep the patient in sight, remove all dangerous objects from the room, and alert the physician or clinician who is responsible for the patient’s care. If the patient answers “no,” the screening test is considered to be a positive test with a potential risk identified. He or she requires a brief suicide safety assessment to determine whether a full mental health evaluation is needed and cannot leave until he or she is evaluated for safety. Alert the physician or clinician who is responsible for the patient’s care. Data are adapted from www.nimh.nih.gov/labs-at-nimh/asq-toolkit-materials/index.shtml#outpatient.

sultation with a psychiatrist should be obtained for a patient with severe depression and urgently in any patient with psychotic symptoms or suicidal thoughts and behavior.

Psychotherapy

Psychotherapeutic interventions are first-line treatments for mild-to-moderate depression.²⁹ A meta-analysis of various psychotherapies, including 53 comparative trials (involving 2757 patients with mild-to-moderate depression) showed that across all forms of psychotherapy, the response rate was 48% (vs. 19% in the control groups).²⁹ No significant differences were noted among various types of psychotherapy, including — but not limited to — cognitive behavioral therapy (identifying and modifying negative thoughts that adversely affect emotion and behavior), be-

havioral activation (scheduling positive activities and increasing positive interactions), and interpersonal psychotherapy (addressing interpersonal issues in a highly structured manner). Another meta-analysis showed significantly higher remission rates among patients who received psychotherapy (i.e., cognitive behavioral therapy [66%], psychodynamic therapy [54%], supportive counseling [49%], and behavioral activation [74%]) than among those in control conditions (43%).³⁰ In order to gain a better sense of the clinical effect, a meta-analysis comparing cognitive behavioral therapy with various control conditions showed a moderate effect size and a number needed to treat of 2.6 to see improvement.³¹ Taken together, the data provide support for cognitive behavioral therapy, interpersonal therapy, and behavioral activation as first-line

treatments for mild-to-moderate depression.³² Data have shown some effectiveness of telephone-based³³ and Internet-based³⁴ psychotherapeutic interventions, and these interventions may be considered, particularly if in-person therapy is not accessible.

The type of psychotherapy should be appropriate for the patient's situation. For instance, interpersonal psychotherapy may help when interpersonal issues are prominent, behavioral activation may increase motivation and initiative, and cognitive behavioral therapy may help to modify distorted thoughts that contribute to depression. If substantive improvement is not seen after 6 weeks of a psychotherapeutic intervention, a change in the type of psychotherapy, initiation of pharmacotherapy, or psychiatric consultation should be considered.

Pharmacotherapy

Antidepressant medications have been a mainstay of treatment for depression, although the favorability of the benefit–risk analysis for milder forms of depression has been questioned.³⁵ A meta-analysis of randomized, placebo-controlled trials of Food and Drug Administration (FDA)–approved antidepressants showed that effect sizes varied according to the severity of baseline depression; effect sizes were small in cases of mild depression but greater in moderate-to-severe depression.³⁶

Although well-controlled randomized trials are the standard for assessing efficacy, it can be challenging to translate these findings into clinical effectiveness; notably, many of these trials are associated with high placebo response rates. Information on “real-world” effectiveness was provided by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, which used a four-level algorithm (reflecting clinical practice at the time) to guide the selection of antidepressant therapies. Citalopram was prescribed as the first (level 1) treatment. If that treatment was unsuccessful, patients underwent randomization to receive alternative therapies within a group of substrategies that the patients had deemed to be acceptable. Level 2 choices included continuation of citalopram, a change to another commonly used medication (sertraline, venlafaxine, or bupropion), or the addition of another medication or cognitive behavioral ther-

apy. Subsequent levels involved switching to or adding less frequently used medications. Treatment with citalopram yielded a response rate of 47% and a remission rate of 37%; the cumulative remission rate of all four levels was 67%.³⁷ The STAR*D trial also showed that none of the antidepressants that were examined were superior to any other and that, after a failed antidepressant trial, switching or augmentation strategies (including with cognitive behavioral therapy) resulted in similar response rates.³⁸

Although the STAR*D trial was limited by the lack of strict randomization and blinding, other analyses have similarly shown no significant differences in efficacy among antidepressant drugs.³⁹ For example, an international, randomized, multicenter trial comparing escitalopram, sertraline, and extended-release venlafaxine showed no significant differences in rates of response at 8 weeks (61%, 66%, and 60%, respectively) or remission (48%, 46%, and 42%, respectively) among the treatments.⁴⁰ A recent meta-analysis of 522 mostly short-term trials involving patients with moderate-to-severe depression showed that all the assessed antidepressants were more effective than placebo (although with modest effect sizes)⁴¹; the same meta-analysis also showed that in head-to-head trials, certain antidepressants (including amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, and vortioxetine) were more effective than others.

For moderate-to-severe depression, first-line medications generally include selective serotonin-reuptake inhibitors (SSRIs), serotonin–norepinephrine-reuptake inhibitors (SNRIs), bupropion, and mirtazapine (Table 2).⁴² Three drugs more recently approved by the FDA for depression — vilazodone, vortioxetine, and levomilnacipran — are also treatment options, but current guidelines (with the exception of the Canadian Network for Mood and Anxiety Treatments [CANMAT] guidelines⁴²) precede these agents. Among the newer agents, the CANMAT guidelines include vortioxetine and milnacipran (a racemic mixture of levomilnacipran and its dextrorotatory enantiomer) as first-line options and vilazodone as a second-line option. Older classes of antidepressants such as tricyclic antidepressants and monoamine oxidase inhibitors have a greater risk profile than newer agents, so they are typically used only if other agents are ineffective.

Table 2. First-Line Antidepressant Medications for Major Depressive Disorder.*

Drug Class and Agent	Dose	Adverse Effects	Clinical Considerations	Indications
SSRIs†				
Fluoxetine	20–80 mg/day	Gastrointestinal and sexual side effects, agitation	Long-acting active metabolites decrease risk of discontinuation syndrome‡; 1-wk washout required when switching to another SSRI or SNRI; increased risk of drug interactions	Major depressive disorder; also FDA-approved for PMDD, OCD, bulimia, panic disorder
Sertraline	50–200 mg/day	Gastrointestinal and sexual side effects, headache; generally acceptable side-effect profile	Risk of sexual side effects higher than with other SSRIs and SNRIs	Major depressive disorder; also FDA-approved for PMDD, OCD, panic disorder, PTSD, social anxiety
Paroxetine	10–60 mg/day	Anticholinergic effects (weight gain, sedation, constipation), gastrointestinal and sexual side effects	Risk of discontinuation syndrome‡; may require slower taper; controlled-release formulation may decrease risk of discontinuation syndrome; increased risk of drug interactions; consider for patients with coexisting depression and anxiety	Major depressive disorder; also FDA-approved for PMDD, OCD, panic disorder, social anxiety, generalized anxiety disorder, PTSD
Fluvoxamine	50–300 mg/day	Anticholinergic effects (weight gain, sedation, constipation), gastrointestinal and sexual side effects, anorexia, insomnia; poor side-effect profile	May have fewer associated sexual side effects than other SSRIs and SNRIs; consider for patients with coexisting depression and anxiety; increased risk of drug interactions	FDA-approved only for OCD; off-label use for major depressive disorder
Citalopram	10–40 mg/day	Gastrointestinal and sexual side effects, sedation; acceptable side-effect profile	Black-box warning regarding doses >40 mg because of QT prolongation	Major depressive disorder; off-label use for anxiety disorders
Escitalopram	5–20 mg/day	Gastrointestinal and sexual side effects	May be associated with a lower risk of headache, dizziness, sedation, and gastrointestinal side effects than other SSRIs and SNRIs; S-enantiomer of citalopram	Major depressive disorder; also FDA-approved for generalized anxiety disorder
SNRIs				
Venlafaxine	37.5–225 mg/day (extended-release formulation) or twice daily (immediate-release formulation, sustained-release formulation)	Agitation, insomnia, tremor, hypertension, tachycardia, sweating, gastrointestinal and sexual side effects, headache, discontinuation syndrome‡	Risk of discontinuation syndrome‡; may require slower taper; extended-release formulation may decrease risk of discontinuation syndrome; may increase energy; may help with anergia or attentional symptoms; risk of death from overdose greater than with other first-line agents	Major depressive disorder; also FDA-approved for generalized anxiety disorder, social anxiety, panic disorder, neuropathic pain
Desvenlafaxine	50–100 mg/day	Agitation, insomnia, tremor, hypertension, tachycardia, sweating, discontinuation syndrome‡	Primary active metabolite of venlafaxine; risk of discontinuation syndrome‡; extended-release formulation may reduce risk of discontinuation syndrome; may increase energy; may help with anergia or attentional symptoms; may need to adjust dose in patients with renal insufficiency	Major depressive disorder; off-label use for anxiety disorders

Duloxetine	60 mg total/day, administered once or twice daily	Agitation, insomnia, tremor, hypertension, tachycardia, sweating	May increase energy; may help with anergia or attentional symptoms; consider for patients with coexisting pain conditions	Major depressive disorder; also FDA-approved for generalized anxiety disorder, diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain
Other agents				
Levomilnacipran	20–120 mg/day	Agitation, sweating, hypertension, tachycardia, palpitations, dysuria	L-enantiomer of milnacipran; may increase energy; may help with anergia or attentional symptoms; fewer gastrointestinal side effects, weight gain, sedation, and sexual dysfunction than SSRIs and SNRIs	Major depressive disorder
Bupropion	50–450 mg/day (extended-release formulation) or twice daily (immediate-release formulation, sustained-release formulation)	Tachycardia, agitation, insomnia, seizures	Consider in combination with SSRI or SNRI; sustained-release and extended-release formulations allow for less frequent dosing and may increase adherence than immediate-release formulation; may help with anergia or attentional symptoms; 0.4% increased risk of seizure at approved doses; contraindications include seizure disorder, bulimia or anorexia, alcohol or benzodiazepine withdrawal; not associated with sexual dysfunction	Major depressive disorder; also FDA-approved as aid to smoking cessation; extended-release formulation indicated for prophylaxis of seasonal depression; may be helpful for ADHD, attention problems, or anergia symptoms
Mirtazapine	15–45 mg/day	Sedation, increased appetite, weight gain	Consider in combination with SSRI or SNRI; consider for patients with coexisting depression and anxiety; lower dose may be more sedating; consider bedtime administration if insomnia or low appetite are present; should not be used if weight gain is an issue; associated with less sexual dysfunction than SSRIs or SNRIs and may aid in SSRI-induced sexual dysfunction	Major depressive disorder; off-label use for anxiety disorders
Vilazodone	10–40 mg/day	Gastrointestinal side effects, insomnia	Associated with less sexual dysfunction than SSRIs and SNRIs; should be taken with food	Major depressive disorder
Vortioxetine	10–20 mg/day	Gastrointestinal and sexual side effects, dry mouth	Effective in patients with cognitive dysfunction from major depressive disorder	Major depressive disorder, cognitive impairment (may improve processing speed)
Agomelatine	25–50 mg/day	Headache, gastrointestinal side effects, fatigue, back pain, anxiety, abnormal dreams, weight gain	May help to normalize sleep cycle (melatonin agonist); increased risk (1–3%) of transaminitis; liver function should be checked at baseline, at adjustment of dose (at 3, 6, 12, and 24 wk), and thereafter when clinically indicated	Major depressive disorder; not available in United States

* ADHD denotes attention deficit–hyperactivity disorder, FDA Food and Drug Administration, OCD obsessive–compulsive disorder, PMDD premenstrual dysphoric disorder, PTSD post-traumatic stress disorder, SNRI serotonin–norepinephrine-reuptake inhibitor, and SSRI selective serotonin reuptake inhibitor.

† SSRIs may increase the risk of bleeding and should be used with caution in combination with nonsteroidal antiinflammatory drugs, aspirin, or other anticoagulants, or in patients who are at risk for bleeding.

‡ The discontinuation syndrome may involve flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances, and hyperarousal.

The selection of an antidepressant is guided by adverse-effect profiles as well as by the patient's coexisting psychiatric disorders, specific symptoms, and treatment history.⁴³ A goal should be to minimize adverse effects, particularly those that might exacerbate existing symptoms or other medical conditions. For instance, drugs commonly associated with increased sedation (e.g., mirtazapine and paroxetine) are not administered during the day in patients with daytime fatigue; conversely, for patients with difficulty sleeping, these sedating drugs may be prescribed at bedtime to promote sleep. Patients with coexisting anxiety are often treated with SSRIs or SNRIs, whereas bupropion and levomilnacipran are generally not used (Table 2). Treatment selection should also include consideration of the patient's personal and family history of medication response and side effects, his or her drug preference, and cost and accessibility (i.e., insurance coverage).⁴⁴

Medication trials generally begin at a low dosage, with dose adjustments typically occurring every 2 weeks. Although improvement may be noted at as early as 2 weeks, full relief of symptoms may not be seen for 8 to 12 weeks (at an adequate dosage). If the initial trial does not yield substantive improvement, switching to another first-line antidepressant (of the same or a different class) is appropriate. Psychotherapy should also be considered, since the combination of drug therapy and psychotherapy has been shown to be more effective than drug therapy alone.⁴⁵ If partial improvement is noted at the maximally tolerated dose, adding an antidepressant of a different class or targeting residual symptoms with other treatments may be an appropriate next step. Psychiatric consultation is recommended if combined therapy or use of a treatment option other than first-line therapy is being considered. Once remission is achieved, maintenance antidepressant treatment to decrease the risk of relapse should generally be continued for at least 6 months.⁴⁶ For persons with a high risk of relapse (e.g., two or more past episodes, residual symptoms, or a history of prolonged or severe symptoms), maintenance treatment should be considered for 2 years or more.⁴⁷ Recurrence of symptoms is common after an index episode; longitudinal studies have shown recurrence rates of 26% within 1 year and 76% within 10 years.⁴⁸

In general, first-line antidepressants have a

manageable side-effect profile (Table 2). One potentially severe adverse effect associated with SSRIs and SNRIs is the serotonin syndrome, which is characterized by agitation, confusion, fever, and tremors that may proceed in severe cases to seizures, coma, and death. Although this syndrome is very rare, the risk may be higher when other drugs that elevate serotonergic tone (e.g., monoamine oxidase inhibitors, tricyclic antidepressants, tramadol, triptans, ondansetron, and metoclopramide) are used in combination with SSRIs and SNRIs.

In 2004, the FDA issued a black-box warning that all SSRIs and venlafaxine were associated with an increased risk of suicidality among persons younger than 24 years of age (www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM173233.pdf). However, other independent reviews have not confirmed this association.⁴² Assuming that appropriate monitoring practices — including those for suicidality — are in place, the risks of untreated depression among adults of any age outweigh the risks of drug treatment.⁴⁴

AREAS OF UNCERTAINTY

Investigators have begun to identify subtypes of depression on the basis of clinical features⁴⁹ or findings on functional magnetic resonance imaging,⁵⁰ as well as on the basis of genetic risk factors⁵¹ and other potential predictors of treatment response⁵²; however, more studies are needed before specific biomarkers or predictors of response may be used to provide clinically valuable information. Pharmacogenomic testing has been suggested to guide dosing and minimize potential dose-related side effects, but evidence that this information aids in predicting treatment response or improves cost-effectiveness is lacking.⁵³

GUIDELINES

Three treatment guidelines for depression — by the American Psychiatric Association,⁴⁴ the CANMAT,⁵⁴ and the National Institute for Health and Care Excellence (United Kingdom)⁵⁵ — offer similar guidance, although only the CANMAT guidelines address recent antidepressant medications. The recommendations in this article are generally concordant with these guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient in the vignette meets the criteria for a major depressive episode. Although her depressive symptoms are not completely debilitating, she has substantial distress that is affecting her functioning; this suggests an episode of moderate severity. We would review her medical history and medications and ask about substance use to rule out potential causes of or contributors to her depressive symptoms. A careful history is also needed to assess evidence of mania or hypomania, since treatment for bipolar depression would differ from that for major depressive disorder. She should be immediately evaluated for possible suicidality to establish that she has no active plans to harm herself and to ensure that she agrees to seek emergency treatment if such feelings develop.

Pharmacotherapy, psychotherapy, or both are all reasonable treatment options for moderate depression. In this patient, given that symptoms have been present for several months, we would recommend a combination of first-line pharmacotherapy and psychotherapy. We would initiate sertraline, which is cost-effective and generally has an acceptable side-effect profile, starting at

50 mg daily and increasing by 50 mg every 2 weeks to a maximum dose of 200 mg, while monitoring for effectiveness and adverse effects. We would discuss effective psychotherapeutic approaches but would favor interpersonal therapy so that the patient could begin to address the relationship conflicts with her partner. If her symptoms completely remit, we would recommend that she continue the use of medication for at least 6 months before considering discontinuation.

Dr. Zarate reports holding patents (PCT/US2007/06898; 8,785,500; 9,539,220; and 9,592,207) on intranasal administration of ketamine to treat depression, patents (PCT/US2012/060256; 9,867,830; and 6296985) on the use of (2R, 6R)-hydroxynorketamine, (S)-dehydroxynorketamine, and other stereoisomeric dehydro and hydroxylated metabolites of (R,S)-ketamine in the treatment of depression and neuropathic pain, pending patent (PCT/US2017/024238) on methods of using (2R, 6R)-hydroxynorketamine and (2S, 6S)-hydroxynorketamine in the treatment of depression, anxiety, anhedonia, fatigue, suicidal ideation, and post-traumatic stress disorder, and pending patent (PCT/US2017/024241) on crystal forms and methods of synthesis of (2R, 6R)-hydroxynorketamine and (2S, 6S)-hydroxynorketamine. No other potential conflict of interest relevant to this article was reported.

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